ACUTE TOXICITY SUMMARY

METHYL ETHYL KETONE

(2-butanone, 3-butanone, methyl acetone, ethyl methyl ketone)

CAS Registry Number: 78-93-3

I. Acute Toxicity Summary (for a 1-hour exposure)

Inhalation reference exposure level	**13,000 μg/m³**
Critical effect(s)	eye, nose and throat irritation in human volunteers
Hazard Index target(s)	Eyes; Respiratory System

II. Physical and Chemical Properties (HSDB, 1993 except as noted)

Description	colorless liquid
Molecular formula	C_4H_8O
Molecular weight	72.10
Density	0.805 g/cm^3 @ 20°C
Boiling point	79.6°C
Melting point	-86.3°C
Vapor pressure	77.5 mm Hg @ 20°C
Flashpoint	-9°C (closed cup)
Explosive limits	1.4% - 11.4%
Solubility	soluble in alcohol, ether, acetone benzene and water
Odor threshold	16 ppm (geometric mean) range = 2-85 ppm (AIHA, 1989)
Odor description	sweet, sharp odor (AIHA, 1989)
Metabolites	2-butanol, 2,3-butanediol (NIOSH, 1978)
Conversion factor	1 ppm = 2.94 mg/m³ @ 25°C

III. Major Uses or Sources

Methyl ethyl ketone (MEK) is a solvent often found in mixtures with acetone, ethyl acetate, n-hexane, toluene, or alcohols. MEK has applications in the surface coating industry and in the dewaxing of lubricating oils. MEK is used in the manufacture of colorless synthetic resins, artificial leather, rubbers, lacquers, varnishes, and glues.

IV. Acute Toxicity to Humans

Symptoms of acute MEK exposure include irritation of the eyes, nose, and throat (HSDB, 1993). In human case studies, inhalation of MEK for its euphoric effect has also resulted in slight excitement, followed by somnolence or unconsciousness at higher concentrations (Glatt, 1977). Humans occupationally exposed to MEK have also complained of mild neurologic effects

including headaches, dizziness, and nausea (Markey, 1991). However, these exposures were to multiple solvents. Human volunteers exposed to pure MEK did not report these symptoms.

In a chamber study, ten human subjects exposed to 100 ppm (300 mg/m³) MEK for 3 to 5 minutes experienced mild throat and nose irritation (Nelson *et al.*, 1943). Mild eye irritation was reported by subjects exposed to 200 ppm (600 mg/m³) for the same duration.

Another chamber study exposed 4 subjects to an increasing concentration of MEK (90 to 270 ppm) over a period of 2 hours (Nakaaki, 1974). The average concentration was 150 ppm for the 2-hour exposure. A relatively strong odor was noted at 90 ppm, upon entry into the room. The odor was described as unpleasant and irritating, but apparently was never offensive enough for the subjects to consider leaving the room early. Irritation of eyes, nose, and throat became more severe as the concentration increased, which eventually led to lacrimation and sneezing sometime during the exposure.

Volunteer subjects were exposed to 200 ppm MEK for 5 minutes followed by 4 hours air or 200 ppm MEK for a total of 4 hours (Dick *et al.*, 1992). Neurobehavioral tests were performed at 2 and 4 hours of exposure and 90 minutes post-exposure. No consistent, statistically significant, neurobehavioral effects were observed. Data on sensory and irritant effects show a significant increase only in perception of strong odor. Therefore, this study identifies a 2-hour free-standing NOAEL of 200 ppm.

In an earlier chamber study by the same research group, human subjects exposed to 200 ppm (600 mg/m³) MEK for 4 hours showed no significant effects as measured by psychomotor, sensorimotor, neurophysiological, and psychological tests (Dick *et al.*, 1989). Effects of exposure on mucous membrane irritation or symptoms such as headache or nausea were not examined in this study.

Predisposing Conditions for Methyl Ethyl Ketone Toxicity

Medical: Persons with preexisting eye or neurologic or skin or respiratory conditions may be more sensitive to the toxic effects of MEK (Reprotext, 1999).

Chemical: Persons exposed to isobutanol may be more sensitive to MEK exposure because MEK is a metabolite of isobutanol (Reprotext, 1999). MEK can potentiate the neurotoxic effects of n-hexane and methyl butyl ketone. MEK may also potentiate the hepatotoxic effects of carbon tetrachloride.

V. Acute Toxicity to Laboratory Animals

The 5-minute RD_{50} in mice for MEK is reported as 10,745 ppm (32,000 mg/m³) (De Ceaurriz, 1981). Pozzani *et al.* (1959) determined an 8-hour LC_{50} in rats to be 23.5 mg/l (7,993 ppm). A 2-hour LC_{50} of 40,000 ppm in mice has been reported (Izmerov *et al.*, 1982).

In a time-to-incapacitation and time-to-death study by Patty *et al*. (1935), exposure to 10,000 ppm of MEK produced incoordination in guinea pigs 90 minutes into exposure. Unconsciousness occurred in all animals between 240 and 280 minutes into exposure. At 33,000 ppm, incoordination occurred 18-30 minutes into exposure and unconsciousness occurred 48-90 minutes into exposure. At 100,000 ppm, incoordination was observed in 3-5 minutes and narcosis in 10-11 minutes. All guinea pigs (6 animals per group) exposed to 33,000 and 100,000 ppm MEK died 200-260 and 45-55 minutes into exposure, respectively. However, lower concentrations (3,300 and 10,000 ppm) did not cause any deaths during exposures up to 13.5 hours. There were no delayed deaths in the guinea pigs that survived exposure (i.e., all deaths occurred during exposure). Death was due to narcosis; lung edema was cited as secondary to the narcosis. Congestion of liver, kidneys and other organs were also noted at lethal concentrations of MEK.

VI. Reproductive or Developmental Toxicity

No studies on the reproductive effects of MEK in humans were available. An increase in the incidence of congenital central nervous system defects was observed among women exposed to a mixture of organic solvents during the first trimester of pregnancy; but MEK alone was not implicated (Holmberg, 1979).

Pregnant rats were exposed to 0, 1,000, or 3,000 ppm MEK for 7 hours per day on days 6-15 of gestation (Schwetz *et al*., 1974). Statistically significant reductions in fetal body weight and in crown-rump length were observed in the 1,000 ppm group but not in the 3,000 ppm group. The incidence of skeletal anomalies was 95% (21 of 23 litters affected) in the 1,000 ppm group. In the 3,000 ppm exposure group, 4 of 21 litters exhibited gross anomalies (two brachygnathous and two acaudate fetuses) which were significantly elevated as compared to controls. A statistically significant increased incidence in delayed sternebral ossification was also observed in the 3,000 ppm exposure group as was a statistically significant increase in total soft tissue anomalies. No signs of maternal toxicity were observed.

To confirm the findings by Schwetz *et al*. (1974), the same research group conducted a similar, but more extensive, developmental study in which pregnant rats were exposed to 0, 400, 1,000, or 3,000 ppm MEK for 7 hours per day on gestational days 6-15 (Deacon *et al*., 1981). The dams exhibited decreased weight gain and increased water consumption during exposure. Two types of minor skeletal malformations were observed in litters of rats exposed to 3,000 ppm MEK, which indicated slight fetotoxicity at this level. No adverse effects were observed in either generation following exposure to 400 or 1,000 ppm. Taken together, the authors of the 2 studies (Schwetz *et al*. 1974; Deacon *et al*., 1981) concluded that the LOAEL for developmental toxicity in rats was 3,000 ppm.

A later study (Schwetz *et al*., 1991) exposed pregnant mice to 0, 400, 1,000, or 3,000 ppm MEK 7 hours per day on days 6-15 of gestation. Relative liver and kidney weights were statistically significantly increased in dams exposed to 3,000 ppm MEK. Decreased fetal weight was also observed in this exposure group; significant decreases were observed in the male fetuses only. A statistically significant trend in the incidence of misaligned sternebrae (a developmental variation)

was observed. The authors concluded that the effects observed in mice were similar and not contradictory to those observed in rats.

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Reference Exposure Level (protective against mild adverse effects): 13,000 μg/m³

Study	Nakaaki (1974)
Study population	4 healthy human volunteers
Exposure methods	inhalation chamber
Critical effects	subjective reports of eye, nose, and throat irritation; lacrimation and sneezing
LOAEL	270 ppm
NOAEL	not reported
Exposure duration	2 hours
Extrapolated 1-hour concentration	270 ppm (not extrapolated; see below)
LOAEL uncertainty factor	6 (mild irritation)
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	60
Reference Exposure Level	4.5 ppm (13 mg/m³; 13,000 μg/m³)

Nakaaki (1974) reported that eye, nose, and throat irritation was produced in subjects exposed to an increasing concentration of MEK (90 to 270 ppm) over a 2-hour period. Lacrimation and sneezing also occurred during exposure but the precise duration and concentration required to produce these effects were unspecified. Because of the uncertainties in determining a precise duration of exposure leading to onset of symptoms, no time-adjustment was used.

In another study, no consistent significant neurobehavioral effects were observed in human volunteers exposed to 0 or 200 ppm MEK for a total of 4 hours (Dick *et al*., 1992). Neurobehavioral tests were administered after 2 and 4 hours of exposure and 90-minutes post-exposure. This study identifies a 4-hour free-standing NOAEL for irritation and neurobehavioral effects of 200 ppm. Personal communications with the principal author indicated that this study should not be used, since it was not designed to address irritation thresholds. In addition, the result from the Dick *et al*. (1992) study contradicts the findings of Nelson *et al*. (1943) which reported a 3-minute LOAEL for irritation of 200 ppm. However, the Dick *et al*. (1992) study contained more accurate measurements of MEK, a longer duration of exposure, and a more sophisticated evaluation of irritation than Nelson *et al*. (1943). Control incidences were very high in the Dick *et al*. study and may preclude the determination of a nuisance effect due to MEK.

While it is apparent that the subjects in the Nakaaki study experienced mucous membrane irritation from MEK during exposure, the nature of the study complicates the determination of the NOAEL and LOAEL for irritant effects. It is unclear from the study whether the lowest concentrations of MEK, starting at 90 ppm, resulted in anything other than odor perception. However, by the end of the 2-hour exposure it was clear that the subjects were experiencing mucous membrane irritation. Based on the known concentration of MEK at the end of exposure (270 ppm), it can be reliably determined that a 2-hour exposure to this concentration will produce

mild irritant effects. Therefore, the LOAEL for the Nakaaki study is 270 ppm while the NOAEL is undetermined.

Level Protective Against Severe Adverse Effects

Based on the findings of the three developmental toxicity studies (Schwetz *et al*., 1974; Deacon *et al*., 1981; Schwetz *et al*., 1991), the NOAEL and LOAEL for maternal and fetal toxicity in rats and mice were determined to be 1,000 and 3,000 ppm, respectively. Maternal toxicity consisted of decreased weight gain and increased water consumption in rats, and increased relative liver and kidney weights in mice. Fetal toxicity consisted of increased incidences of gross and skeletal anomalies and delayed sternebral ossification in rats, and decreased fetal weight in mice. The highest actual time-weighted-average NOAEL among the three studies was 1,126 ppm (Schwetz *et al*., 1974). The 7-hour per day exposure concentration was used as the basis for the level protective against severe adverse effects with no time extrapolation. An uncertainty factor of 10 was applied to the adjusted NOAEL to account for interspecies differences. An additional uncertainty factor of 10 was applied to account for sensitive individuals, which results in a level protective against severe adverse effects of 11 ppm (32 mg/m^3) for 7-hour exposure to MEK.

Level Protective Against Life-threatening Effects

Human exposure data relevant to a life-threatening level determination for MEK could not be found in the literature. Therefore, LC_{50} studies in experimental animals provided the best source for a life-threatening effect level in humans. Only one citation (LaBelle and Brieger, 1955) was located in the literature that contained sufficient mortality data from which to estimate an LC_{50}, MLE_{05} (maximum likelihood estimate, corresponding to 5% mortality), BC_{05}, and BC_{01} (benchmark dose at the lower 95% confidence interval expected to produce a response rate of 5% and 1%, respectively) by log-normal analysis (Crump, 1984; Crump and Howe, 1983). The results are shown below in Table 1. Rats (4 to 8 per group) were exposed for 4 hours by inhalation to concentrations of MEK ranging from 7,850 to 20,200 ppm. Acute toxicity resulted in narcosis with most deaths occurring immediately (i.e., occurring during exposure).

Table 1. Rat Lethality Benchmark Dose Determination from LaBelle and Brieger (1955) for 4-hour Methyl Ethyl Ketone Exposure.

LC_{50} (ppm)	MLE_{05} (ppm)	BC_{05} (ppm)	BC_{01} (ppm)	BC_{05} (ppm) Adjusted to 1 hour
11,600	8,559	7,062	5,790	14,124

Based on log-normal probit analysis of the lethality data by LaBelle and Brieger (1955), the BC_{05} was determined to be 7,062 ppm (see Table 1). The BC_{05} was then adjusted to 1 hour exposure using a modification of Haber's equation ($C^n * T = K$), where the exponent n = 2 (for extrapolation of exposure duration greater than 1 hour to 1 hour exposure). The resulting concentration at the BC_{05} for 1 hour exposure was 14,124 ppm. An uncertainty factor of 3 was applied to account for interspecies differences because the BC_{05} likely accounts for some degree

of variability and an uncertainty factor of 10 was applied to account for the increased susceptibility of sensitive human individuals. The total UF was 30.

$$\text{level protective against life-threatening effects} = BC_{05}/(UF)$$

Incorporation of these factors results in a level protective against life-threatening effects of 471 ppm (1,385 mg/m³**)** for 1-hour exposure to MEK.

VIII. References

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